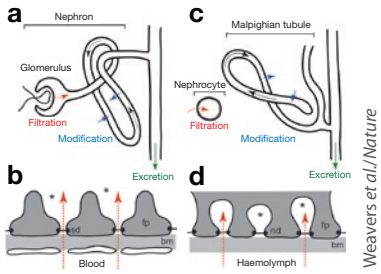
Kidney International (2009) **75,** 349–350. doi:10.1038/ki.2008.656

Podocyte-like cell with filtration slit diaphragm in insects



Schematic drawings of the (**a**) vertebrate nephron, (**b**) glomerular filtration barrier, (**c**) insect excretory system, and (**d**) nephrocyte filtration barrier. Ultrafiltration (red arrows), filtrate flow (black arrows), and urinary space (**b**, asterisks) or extracellular lacunae (**d**, asterisks) are shown. bm, basement membrane; fp, foot process; nd, nephrocyte diaphragm; sd, slit diaphragm.

Although the fully developed nephron has long been regarded as a vertebrate adaptation, 'nephron-like' features can be found in the excretory systems of many invertebrates. In vertebrates, the podocytes in the glomerular filtration barrier send out interdigitating foot processes to enwrap the glomerular capillaries. These processes are separated by 30- to 50-nm-wide slit pores spanned by the slit diaphragm that, together with the glomerular basement membrane, form a size- and charge-selective filtration barrier. The invertebrate excretory systems contain filtration cells and ducts in which the filtrate is modified, and insect nephrocytes regulate hemolymph composition by filtration, followed by endocytosis and processing to sequester and/or secondarily metabolize toxic materials (Figure). In *Drosophila*, nephrocytes are tethered to the esophagus or heart and are bathed in hemolymph, and extensive infolding of their plasma membrane generates a network of labyrinthine channels or lacunae flanked by nephrocyte foot processes. The channel entrances are narrow slits 30 nm in width, spanned by a single or double filament forming a specialized filtration junction—the nephrocyte diaphragm. The similarities between the anatomies of the nephrocyte and podocyte filtration barriers led Weavers *et al.* to investigate whether the nephrocyte diaphragm is molecularly related to the slit diaphragm. In *Drosophila melanogaster*, they found that orthologues of the major constituents of the slit diaphragm, including nephrin, NEPH1, CD2-associated protein, zonula occludens-1, and podocin, were expressed in the nephrocyte and form a complex of interacting proteins that closely mirrors the vertebrate slit diaphragm complex. Furthermore, they found that the nephrocyte diaphragm was completely lost in flies lacking the orthologues of nephrin or NEPH1—a phenotype resembling loss of the slit diaphragm in the absence of either nephrin or NEPH1. The similarities between invertebrate nephrocytes and vertebrate podocytes suggest that the two cell types are evolutionarily related and establish the nephrocyte as a simple model in which to study podocyte biology and podocyte-associated diseases. (*Nature* advance online publication, 29 October 2008; doi:10.1038/nature07526)

Juan Oliver

Irbesartan in patients with heart failure and preserved ejection fraction

Trials have shown that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) improve cardiovascular outcomes in several populations without kidney disease. However, investigations of these agents in patients on dialysis have yielded conflicting results. Early data in a trial of dialysis patients suggested that an ACEI lowered mortality,[1] whereas a later study demonstrated that patients with kidney disease did not benefit as much as patients with normal kidney function.[2] Now, a new study by Massie *et al.* evaluates the effect of the ACEI irbesartan among patients with heart failure and preserved ejection fraction. More than 4000 subjects at least 60 years of age with class II, III, or IV heart failure and an ejection fraction of at least 45% were randomly assigned to receive 300 mg of irbesartan or placebo per day. The primary outcome of death from any cause or hospitalization for a cardiovascular cause occurred in 742 patients in the irbesartan group and 763 in the placebo group (95% confidence interval (CI), 0.86–1.05; $P = 0.35$). The hazard ratio was 1.00 (95% CI, 0.88–1.14; $P = 0.98$) for mortality and 0.95 (95% CI, 0.85–1.08; $P = 0.44$) for hospitalization.

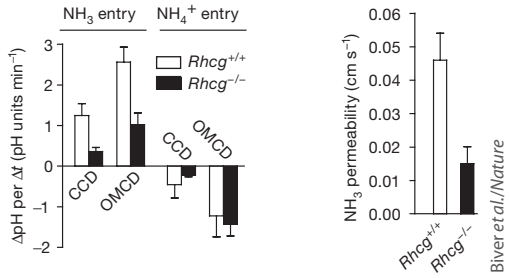
Conclusions from this trial of patients with normal kidney function cannot be applied to patients on dialysis. However, they reveal that acute heart failure is an outcome instead of a disease or syndrome, and that treatments likely do not function similarly across all etiologies. Therefore, the cause of the heart failure needs to be considered carefully before a treatment is chosen or a trial design is formulated. (*N Engl J Med* 2008; **359**: 2456–2467; doi:10.1056/NEJMoa0805450)

Lynda Szczech

[1]*Am J Kidney Dis* 2008; **52**: 501–506. [2]*Kidney Int* 2006; **70**: 1318–1324.

A new renal NH_3 transporter

Renal ammonium production and excretion are essential for net acid excretion in organisms that generate hydrogen (H^+) from their diet. Along the nephron, ammonium is produced in proximal tubular cells, secreted into the proximal urine, then reabsorbed in the thick ascending limb of the loop of Henle. Approximately 80% of the ammonium produced in the proximal tubule is finally secreted into the urine by the collecting duct. Since initially described, the process of transepithelial transport of ammonium in the collecting duct has been thought to occur through non-ionic NH_3 diffusion across the lipid bilayer. NH_3 is then trapped as NH_4^+ in the lumen of the collecting duct by buffering protons secreted throughout ATPases present at the apical membrane of acid-secreting intercalated cells. However, ammonium transporter proteins have been described in microorganisms; the Mep-Amt family of ammonium transporters, in particular, was identified in yeast but also found in other microorganisms as well as plants and invertebrates. Although these proteins are absent in vertebrates, Rhesus (Rh) factors have



Isolated cortical collecting ducts (CCD) and outer medullary collecting ducts (OMCD) *in vitro*. Left: Alkalinization (that is, NH_3 entry) and acidification (NH_4^+ entry) rates in CCD and OMCD cells. The reduced rate of alkalinization in *Rhcg*$^{-/-}$ cells indicates impaired luminal NH_3 entry. Right: NH_3 permeability across *Rhcg*$^{-/-}$ CCD epithelium was strongly impaired compared with wild type.

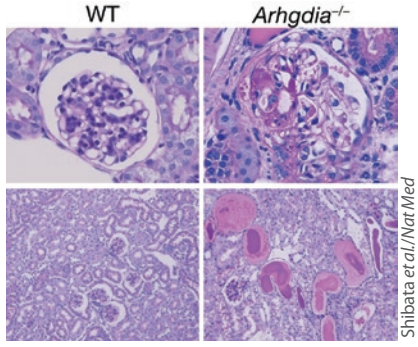
previously been shown to be related to proteins of the Mep-Amt family and could correspond to their yet-to-be-described vertebrate counterpart. The main Rh antigen (RHD) was identified decades ago, but the physiological role of Rhesus-type proteins remains unknown. However, several functional expression studies indicate that Rh proteins can function as ammonium transporters. Human Rh factors comprise blood-group antigens, their associated glycoprotein, and two non-erythroid members (Rhbg and Rhcg), which are found in the distal nephron. In the acid-secreting intercalated cells of the mouse kidney, basolateral Rhbg coexists with apical Rhcg. But genetic ablation of mouse Rhbg did not impair renal ammonium excretion, nor did it yield a phenotype. In a new study, Biver *et al.* targeted the *Rhcg* gene in mice and found that the Rhcg protein is required for urinary ammonium excretion. H_4CL acid load in wild-type mice induced a transient decrease of blood pH and bicarbonate levels with partial recovery 6 days later because of adaptation. In contrast, in *Rhcg*$^{-/-}$ mice, the decrease in blood pH and bicarbonate levels lasted throughout the entire treatment, indicating an impaired ability to cope with the acid load. Further, nonrenal acid excretion was lower in *Rhcg*$^{-/-}$ mice because of a defect in ammoniuria. The authors also found that the net tubular epithelial permeability to NH_3 was impaired in *Rhcg*$^{-/-}$ mice (Figure). Thus, during urinary acidification and ammonium excretion, Rhcg acts as an ammonium transporter, which mediates the net flux of NH_3 in the collecting ducts. This elegant study leads to a new model of renal ammonium excretion wherein NH_3 is at least in part translocated through a protein-mediated pathway, and not only through simple non-ionic diffusion and subsequent luminal trapping, as previously thought. (*Nature* 2008; **456**: 339–343; doi:10.1038/nature07518)

Qais Al-Awqati

Rac1 GTPase regulates the mineralocorticoid receptor and affects proteinuria

The mineralocorticoid receptor has a major pathophysiological role in the progression of kidney diseases and inhibition of its signaling reduces proteinuria. Recent studies have shown cross-talk between steroid receptors and intracellular signaling pathways. One such example is their interaction with the Rho family of small guanosine triphosphate (GTP)ases; Rho family members and their regulatory proteins are involved in the transactivation of several steroid receptors. In a recent study, Shibata *et al.* examined the possibility that Rho GTPases could influence the function of the mineralocorticoid receptor. They found that Rac1, a member of the Rho family of GTPases, is a potent activator of mineralocorticoid receptor signal transduction both *in vitro* and *in vivo*. Transfection assays in cultured human embryonic kidney cells revealed that constitutively active Rac1 (CA-Rac1) enhanced mineralocorticoid receptor-dependent reporter activity, which was accompanied by increased nuclear translocation of mineralocorticoid receptor. Also, CA-Rac1 facilitated mineralocorticoid receptor nuclear accumulation in podocytes via p21-activated kinase phosphorylation. To perform *in vivo* experiments, the authors made use of the fact that Rho GDP dissociation inhibitor (RhoGDI) interacts with the GDP-bound inactive Rho GTPases and prevents them from being converted to the active GTP-bound forms. Three distinct isoforms of RhoGDI exist in mammals: GDI-α, GDI-β, and GDI-γ. Among these, they suspected that RhoGDI-α could have a major role in the kidney, because mice with deletion of its gene (*Arhgdia*$^{-/-}$ mice) develop progressive renal disease. They found that *Arhgdia*$^{-/-}$ mice had mild albuminuria but unselective proteinuria by approximately 4 weeks of age. Renal histology at 1 week of age was normal by light microscopy, but transmission electron microscopy revealed focal effacement of the podocyte foot processes. At 12 weeks of age, *Arhgdia*$^{-/-}$ mice had massive albuminuria and glomerular lesions with focal and segmental sclerosis (Figure). These findings were associated with increased Rac1 (but not RhoA) and mineralocorticoid receptor signaling in the kidney, without alteration in systemic aldosterone. In addition, use of a Rac-specific inhibitor diminished mineralocorticoid receptor overactivity and renal damage. Finally, both histological changes and albuminuria in *Arhgdia*$^{-/-}$ mice were suppressed by mineralocorticoid receptor blockade. These results indicate an important regulating effect of Rac1 on mineralocorticoid receptor activity and identify Rac1 as a potential therapeutic target for chronic kidney and other organ diseases. (*Nat Med* 2008; **14**: 1370–1376; doi:10.1038/nm.1879)

Juan Oliver



Kidneys of wild-type (WT) and *Arhgdia*$^{-/-}$ mice at 12 weeks of age. *Arhgdia*$^{-/-}$ mice showed focal and segmental glomerulosclerosis with prominent proteinaceous casts and tubular dilatation.